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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,174	09/19/2001	William G. Kerr	USF-T150CX	9411

23557 7590 09/26/2006

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,174	KERR, WILLIAM G.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6-28-06 & 7-11-06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-44,46-87 and 90-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-44,46-87 and 90-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-10-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 6-28-06 and 7-11-06.

Claims 38-44, 46-87 and 90-92 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-28-06 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections and New Rejections Necessitated by Amendments

Claims 38-44, 46-87 and 90-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons

of record set forth the Office actions mailed 5-5-05, 12-29-05 and for the reasons set forth below. This is both a new matter rejection and a written description rejection, and the arguments for maintaining both grounds of rejection are set forth below.

The claims are drawn to compositions and methods for reducing SHIP-1 function in human or mouse hematopoietic cells in vivo, and for suppressing rejection of a transplant in a human or mouse, comprising the administration of an interfering RNA (RNAi) specific for SHIP-1 mRNA that is present in human or mouse hematopoietic cells, which RNAi hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells and reduces SHIP-1 function in human or mouse, suppresses graft-versus-host disease in a mouse or human, and suppresses transplant rejection in a human or mouse.

Applicant's arguments filed 6-28-06 have been fully considered but they are not persuasive. Applicant argues that a high degree of homology between mammalian SHIP-1 orthologues and between SHIP-1 isoforms exist and are well known in the art, and that adequate written description of human and mouse SHIP-1 mRNA has been provided in the instant disclosure. Applicant also argues that the knowledge of the sequence and structure of the SHIP gene provides on skilled in the art with sufficient structural and function correlates to describe the genus of RNAi molecules claimed. Applicant is correct that adequate written description has been provided in the instant disclosure and in the art to describe the SHIP-1 target molecules claimed. But, contrary to Applicant's assertions, the description provided of the target molecules claimed and

the subsequent description of two RNAi constructs (filed 7-21-04) that provide for the functions claimed, of reducing SHIP-1 function in human or mouse hematopoietic cells in vivo, and of suppressing rejection of a transplant in a human or mouse, are not representative of the broad genus comprising RNAi that hybridize in vivo with SHIP-1 mRNA present in hematopoietic cells of the human or mouse and reduce SHIP-1 expression therein. The subsequent disclosure of two species within the broad genus of RNAi molecules claimed, that, when combined provide for the treatment effects claimed, are not representative of the very broad genus of inhibitory molecules claimed.

The specification and claims do not adequately describe the concise structural features that distinguish structures within the claimed genus from those without (*e.g.* the nucleotide sequences or a representative number of RNAi molecules of the generic RNAi structures claimed, that specifically bind and inhibit SHIP-1 function in vivo, and which suppress graft-versus-host disease and transplant rejection). One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of the inhibitory molecules claimed, encompassing the genus comprising RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any RNAi that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells and provides the treatment effects claimed.

Applicants argue that the subject specification provides sufficient information regarding the genus of SHIP-1 mRNA as well as interfering RNA specific thereto. Applicant argues that at page 5, lines 27-34 of the instant disclosure, substances that

inhibit SHIP function are expressly taught and that rewording of a passage where the same meaning remains intact does not constitute new matter.

Contrary to Applicant's assertions, the original disclosure (filed 9-19-01) makes no mention of interfering RNA. The declaration filed later in prosecution, on 7-21-04, provides a disclosure of experiments in which SiRNA (*a.k.a.* interfering RNA or RNAi) molecules #1, 2, 3 and 4, or a combination or subcombination of them, were found to successfully inhibit the expression of SHIP-1 in vitro and in vivo. The original application, however, does not provide disclosure of these SiRNA molecules, nor of these experiments, nor of any mention of interfering RNA molecules in general. Applicants provide a supplemental IDS (filed 10-7-05) with various references teaching RNAi molecules and their use in RNAi-mediated gene suppression in mammalian cells. The existence of these publications, however, is no substitute for the original disclosure of this invention in the subject patent application.

Applicant also argues that, while the predictability that any single interfering RNA molecule will be effective in gene silencing is not necessarily high, the probability of identifying an individual functional interfering RNA molecule among candidates is very high... Contrary to Applicant's assertions, the eventual identification of molecules among a myriad of candidate possibilities is no substitute for the requirement of having in one's possession, at the time of filing, a representative number of species for such a broad genus claimed, as in the instant case, for the genus comprising RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or that hybridize in vitro under conditions of stringency with human or mouse SHIP-1 mRNA, or hybridize in vivo

with SHIP-1 mRNA present in mouse or human hematopoietic cells, and reduce SHIP-1 function in human or mouse, or suppress graft-versus-host disease or transplant rejection in a mouse or human. For these reasons, the instant rejection is maintained.

Claims 38-44, 46-82 and 90-92 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth the Office actions mailed 5-5-05, 12-29-05, and for the reasons set forth below.

The claims are drawn to methods for interfering and reducing SHIP-1 function in a human or mouse, for suppressing transplant rejection in a human or mouse, and for suppressing graft versus host disease (GVHD) in a human or mouse comprising the administration any RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or which RNAi hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells.

The instant disclosure, while being enabling for a method of suppressing the rejection of an allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice or abrogating GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, thereby enhancing SHIP-/- mice survival, and while being enabling for the in vivo inhibition of SHIP-1 expression in mice using the RNAi sequences #1, #4 and the mouse antisense vector muSHIPshRNA provided in the declarations by Dr. Kerr, filed 7-21-04 and 2-9-05, does not reasonably provide enablement for inhibiting SHIP-1 in vivo comprising the administration of *any* RNAi

specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising the administration in vivo or ex vivo of *any* nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or that hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells, nor of suppressing a transplant rejection in any patient, or treating graft versus host disease (GVHD) in any patient comprising the administration of any interfering RNA specific for SHIP mouse or human mRNA.

Applicant's arguments filed 6-28-06 and pre-publication article filed 6-28-06 have been fully considered but they are not persuasive. Applicant argues that the instant invention was enabled for the full scope claimed at the time of filing because the data presented by declaration, filed 7-16-04, showed that C57Bl6/J mice injected i.p. on days 1, 2, and 3 with SHIP-1 shRNA vector complexed with the cationic lipid DOTAP resulted in significant suppression of all detectable SHIP-1 isoforms in the spleen, and siRNA molecules complexed with DOTAP and injected i.v. into C57BL6/J mice resulted in partial suppression of SHIP-1 expression in peripheral mononuclear cells and resulted in a significant increase in monocytes and circulating myeloid suppressor cells. Applicant also argues that proper support has been provided in the instant specification for the use of liposomal and vector delivery devices as well.

Applicant is correct that in vivo effects have been demonstrated by the declaration filed on 7-16-04 and that general teachings exist in the instant disclosure for delivery devices for nucleic acids used in organisms.

The specification as filed teaches the suppression of the rejection of an allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice, as well as the abrogation of GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, whereby SHIP-/- mice survival was enhanced. The declarations subsequently filed on 7-21-04 and 2-9-05 teach the in vivo inhibition of SHIP-1 following the co-administration of RNAi sequences #1, #4, or following the administration of the mouse antisense vector muSHIPshRNA.

The ability of co-administered RNAi's, or of the mouse antisense vector muSHIPshRNA to target and successfully inhibit expression of the target gene encoding SHIP1 in a mouse model, and provide for an observed increase in Mac+Gr1 monocytes and circulating Mac1+GR1+cells (myeloid suppressor cells) is not representative or correlative of the ability to achieve in vivo SHIP-1 inhibition of expression or subsequent treatment effects comprising the administration of <u>any</u> RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any nucleic acid molecule (and of any size) that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells. One skilled in the art would not accept on its face the examples given in the specification of the enhanced survival and reduction of transplant rejection in a mouse model using SHIP-/- mice as being correlative or representative of the successful inhibition of expression of SHIP in vivo using interfering RNA specific for SHIP mRNA, and further whereby treatment effects are provided for transplant rejection or graft versus host disease (GVHD) in a patient in view of the lack of guidance in the

specification and known unpredictability associated with the ability to predict the efficacy of interfering RNA in inhibiting the expression of SHIP in a mouse or human in treating, suppression transplant rejection or graft versus host disease (GVHD) in a patient following administration by any route of the claimed RNAi oligoncucleotides.

Applicant argues that Paraiso et al (unpublished manuscript filed 6-28-06) demonstrates that induction of SHIP-deficiency in the adult allogeneic bone marrow transplant enhances both the quality and duration of post-transplant survival and taken with other experimental evidence submitted previously, makes it clear that SHIP deficiency can be induced prior to engraftment and result in enhanced transplant survival and even partial SHIP deficiency (via RNAi) will enhance transplant survival. Applicant is correct that treatment effects have been provided in an organism for a subset of the broad genus of RNAi molecules claimed, and which have been adequately described in the post-filing communications.

The specification as filed, however, fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by the broad genus of RNAi claimed, which treatment methods comprise methods of suppressing graft versus host disease and transplant rejections in a subject comprising any RNAi that specifically hybridizes under stringent conditions the target human or mouse SHIP-1 mRNA. For these reasons, the instant rejection for lacking enablement over the scope claimed, is maintained.

Claim Rejections - 35 USC § 103

Claims 67-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Damen et al and Ware, in view of Fire and Gill et al for the reasons of record set forth the Office action mailed 12-29-05.

Applicant's arguments filed 6-28-06 have been fully considered but they are not persuasive. Applicant argues that no motivation has been providing to combine RNAi with a pharmaceutically acceptable carrier for the in vitro applications recited in the rejection. Contrary to Applicant's assertions, the genus comprising pharmaceutically acceptable carriers includes water, which is most certainly disclosed in all of the references cited in the 103 rejection of record. Furthermore, one of ordinary skill in the art would have been motivated to provide such compositions (including water or a suitable buffer that is pharmaceutically compatible) in order to use RNAi molecules to target and inhibit the expression of SHIP-1 in vitro because Ware et al and Damen both teach the role of SHIP-1 in the modulation of Ras and inositol signaling pathways, and its potential role in such cellular processes is feasibly investigated by inhibiting its expression in vitro using the routine method of oligonucleotide based inhibition, including by antisense or RNAi inhibition. It would have been obvious to design RNAi molecules for inhibiting expression of SHIP-1 in vitro because Fire teaches this routine technique and its enhanced effectiveness in target gene inhibition using these RNAi molecules compared to antisense in target gene inhibition (see e.g. col. 1-3 and Table 1 in col. 22-24 of Fire). Using the teachings of Fire, it would have been routine experimentation to design compositions comprising various RNAi molecules to inhibit the expression of the mouse or human SHIP-1 molecule because the nucleotide

sequences of mouse and human SHIP-1 have been taught previously by Damen and Ware, and Fire teach the routine technique of designing RNAi to target and inhibit the expression of target genes of known sequence. One of ordinary skill in the art would have been motivated to produce the compositions comprising RNAi which target and inhibit the expression human and mouse SHIP-1 in order to study its role in the cellular processes of signaling because Damen and Ware teach the potential role of SHIP-1 in these important cellular processes whose aberrations are being investigated in various pathological conditions or diseases. One of ordinary skill in the art would have been motivated to provide compositions further comprising either viral or plasmid vectors comprising RNAi molecules, and optionally further comprising liposomes, all of which compositions comprise the pharmaceutically compatible diluent of water, because these compositions are routinely used to enhance delivery and subsequent expression of inhibitory oligonucleotides to target cells in vitro for targeting and inhibition of a desired target gene sequence. For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
9-20-06

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